TECHNICAL COMMENTARY

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Parietal lobe

Introduction

The parietal cortex is located posterior to the frontal lobe. It is structurally divided into the superior, middle and inferior gyri. The most anterior portion of the parietal lobe forms the postcentral gyrus, the somatosensory cortex. Posterior to this are the parietal association regions, and the visual regions of the posterior parietal cortex, involved in visuospatial processing.

Schizophrenia has been associated with altered structure and function of the parietal lobe. Understanding of any brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. Reviews contained in this technical summary reflect both structural (MRI, DTI), and functional imaging (fMRI, PET) studies, as well as metabolic investigations (MRS) of the parietal lobe in schizophrenia.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention, or other matter under review, are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 25 systematic reviews that met our inclusion criteria[3-27].

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Structural changes

- Moderate to high quality evidence found decreased parietal grey matter volume in medicated people with schizophrenia compared to controls. There were reductions in the left inferior parietal gyrus in chronic patients, and bilateral postcentral gyrus reductions in both chronic and first-episode patients. Reductions in the right postcentral gyrus were greater in people with chronic schizophrenia than in people with first-episode schizophrenia.
- Moderate to high quality evidence found greater reductions over time (1-10 years) in parietal white matter of people with schizophrenia compared to controls. Parietal grey matter reductions over time were found only in first-episode patients. Increased antipsychotic dose was associated with decreased parietal lobe volume over time (>2 years).
- Moderate to high quality evidence found better overall functioning was associated with larger parietal lobe volume.

Functional changes

- Moderate quality evidence suggests decreased activation in the lower precuneus and the precuneus of people with schizophrenia at rest compared to controls at rest. Relatives of people with schizophrenia also had decreased resting-state activity in the left precuneus.
- Moderate to low quality evidence found increased activation in the postcentral gyrus and the inferior parietal lobule during auditory hallucinations.
- Moderate quality evidence found decreased functional activation in the right inferior parietal lobe of people with schizophrenia compared to controls during episodic memory encoding and executive functioning. The left inferior parietal cortex of people with schizophrenia showed increased activity during executive functioning and theory of mind tasks and decreased activity during cognitive control tasks. The right inferior parietal cortex of people with schizophrenia showed increased activity during theory of mind tasks. The left postcentral gyrus showed increased activity during episodic memory encoding. Bilateral superior parietal gyri showed increased activity during timing tasks and increased activity in the parietal cortex in general during inhibition and emotion tasks.
- Moderate quality evidence found increased activity in relatives of people with schizophrenia compared to controls in the left inferior parietal gyrus and the left precuneus during executive functioning and working memory tasks, increased activity in the right parietal precuneus and right inferior parietal lobule during cognitive tasks. There was decreased activity in relatives in the right parietal cortex during executive functioning tasks. During emotion tasks, there was increased activation in relatives in the left sub-gyral parietal region and the left precuneus, and decreased activation in relatives in the right inferior parietal lobule.
- Moderate to low quality evidence found increased activity in the right superior parietal lobe and the right postcentral gyrus after cognitive remediation.
- Moderate quality evidence found increased activation during facial emotion recognition in the left inferior parietal region of people with schizophrenia compared to people with an autism spectrum disorder.
- Moderate quality evidence found no differences in NAA or GABA levels between people with schizophrenia and controls.

Structural and functional changes

- Moderate quality evidence found decreased grey matter volume and decreased functional activity in the left inferior parietal gyrus of drug-free patients. There was increased grey matter volume and

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decreased functional activity in the right inferior parietal gyrus.

- Moderate to low quality evidence found reduced grey matter volume in the left postcentral and inferior parietal lobe was associated with increased severity of neurological soft signs in patients. Neurological soft sign severity correlated with increased activation in the right precuneus.

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Alustiza I, Radua J, Pla M, Martin R, Ortuno F

Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Functional activation during cognitive control tasks in people with schizophrenia vs. controls.** **Cognitive control is defined as the level of perceived difficulty of the cognitive task and the subsequent mental effort that an individual applies to achieve the cognitive aim.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) found decreased activation during cognitive control tasks in the left inferior parietal gyrus. During timing tasks, there was increased activation in bilateral superior parietal gyri.**
Functional activation	
Cognitive control tasks 29 studies, N = 2,268 *Significant, decreased activation in people with schizophrenia was found in;* Left inferior parietal gyrus (BA 40) Timing tasks 8 studies, N = 395 *Significant, increased activation in people with schizophrenia was found in;* Bilateral superior parietal gyri (BA 7)	
Consistency in results‡	Unable to assess; no measure of consistent is reported.
Precision in results§	Unable to assess; no measure of precision is reported (CIs).
Directness of results‖	Direct

Brugger S, Davis JM, Leucht S, Stone JM

Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis

Biological Psychiatry 2011; 69: 495-503

View review abstract online

Comparison	**N-acetyl aspartate (NAA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, consistent, direct, unable to assess precision) suggests no differences in NAA levels.**
NAA	
Parietal lobe *No difference between people with schizophrenia (all patients) and controls;* 5 studies, N = 175, *d* = -0.08 95%CI not reported, *p* = 0.62, Q = 2.83, *p* = 0.97, I^2 = 0%	
Consistency in results	Consistent apart from frontal lobe and temporal lobe data.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1) 177-188

View review abstract online

Comparison	**Grey matter changes in people with schizophrenia vs. controls.**

Parietal lobe

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with first-episode schizophrenia have grey matter reductions in bilateral postcentral gyrus. People with chronic schizophrenia have reductions in the right postcentral gyrus which was greater than in first-episode schizophrenia.**
Parietal grey matter volume	
Areas of reduced volume in first-episode schizophrenia; 14 studies, N = 1,082 Right postcentral gyrus Talairach coordinates 52, -20, 44, cluster 216mm^3, ALE 0.0115 Left postcentral gyrus Talairach coordinates -60, -18, 20, cluster 200mm^3, ALE 0.0117 *Areas of reduced volume in chronic schizophrenia;* 19 studies, N = 1,664 Right postcentral gyrus: Talairach coordinates 56, -20, 18, cluster 792mm^3, ALE 0.0239 *Subtraction analysis showed greater grey matter reductions in the chronic group than in the first-episode group in;* Right postcentral gyrus: Talairach coordinates 56, -22, 16, cluster 160mm^3, ALE 0.0151	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P

Altered Hub Functioning and Compensatory Activations in the Connectome: A Meta-Analysis of Functional Neuroimaging Studies in Schizophrenia

Schizophrenia Bulletin 2016; 42: 434-42

View review abstract online

Comparison	**Functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests during emotion and inhibition**

	tasks, there was over-activation in the parietal cortex.
Functional activation	
314 studies, N = 10,942 Inhibition tasks and emotion tasks Over-activation in the parietal cortex.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Egerton A, Modinos G, Ferrera D, McGuire P

Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis

Translational Psychiatry 2017; 7: e1147

View review abstract online

Comparison	**GABA levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, imprecise, direct) finds no differences in GABA levels.**
GABA	
No significant differences between groups; Parietal/occipital cortex 6 studies, N = 250, g = -0.30, 95%CI -0.90 to 0.03, p = 0.30, I^2 = 80% There were no moderating effects of diagnosis (first-episode psychosis vs. schizophrenia), age, illness duration, symptom severity, %grey matter or publication date.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C

Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies

Schizophrenia Research 2009; 108(1-3): 104-113

View review abstract online

Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in the left inferior parietal gyrus of people with schizophrenia.**
Parietal grey matter volume	
37 studies, N = 3,336 Decreased grey matter was reported in the left inferior parietal gyrus. *Clusters where volume reductions were significantly more frequent than grey matter concentration reductions (grey matter as a proportion of the whole brain volume);* Right precentral and postcentral gyri: Talairach coordinates 52.97, -24.28, 43.55, Voxel cluster size 408mm^3, ALE -0.54 x 10^{-3}	

Gao X, Zhang W, Yao L, Xiao Y, Liu L, Liu J, Li S, Tao B, Shah C, Gong Q, Sweeney JA, Lui S

Association between structural and functional brain alterations in drug-free patients with schizophrenia: A multimodal meta-analysis

Journal of Psychiatry and Neuroscience 2018; 43: 131-42

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs. controls.** **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent,**

	direct, unable to assess precision) suggests decreased grey matter volume and decreased functional activity in the left inferior parietal gyrus of drug-free patients. There was increased grey matter volume and decreased functional activity in the right inferior parietal gyrus.
Structural and functional alteration	
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant decreased grey matter volume and decreased functional activity in;* Left inferior parietal gyrus: 333 voxels, MNI coordinates -52, -44, 44, $p < 0.001$ *Significant increased grey matter volume and decreased functional activity in;* Right inferior parietal gyrus: 100 voxels, MNI coordinates 42, -56, 46, $p < 0.001$	
Consistency in results	Authors report most findings were consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT

Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis

Biological Psychiatry 2008; 64(9): 774-781

View review abstract online

Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in the left postcentral gyrus of people with schizophrenia.**
Parietal grey matter volume	
13 studies, N = 2,457 *Clusters where density reductions were more frequent in people with schizophrenia than in controls;* Left postcentral gyrus: Talairach coordinates -62, -16, 18, Voxel cluster size 608mm^3, $p < 0.01$, ALE =	

0.012	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Goghari MV

Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimate meta-analysis

Psychological Medicine 2001; 41: 1239-1252

View review abstract online

Comparison	**Functional activation during executive functioning and working memory tasks in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests increased activity in relatives in the left inferior parietal gyrus and left precuneus during executive functioning and working memory tasks. There was also decreased activity in relatives in the right parietal cortex during executive functioning tasks.**
Functional activation	

Parietal lobe

17 studies, N = 456 *Increased activity during executive functioning in relatives in;* Left inferior parietal gyrus: Talairach coordinates -40/-40, -64/-60, 46/44, cluster volume 192 mm^3 Left precuneus: Talairach coordinates -2, -80, 44, cluster volume 368 mm^3 *Decreased activity during executive functioning in relatives in;* Right parietal cortex: Talairach coordinates 24, -48, 42, cluster volume 144 mm^3 *Increased activity during working memory in relatives in;* Left inferior parietal cortex: Talairach coordinates -40/-40, -64/-60, 46/44, cluster volume 264 mm^3 Left precuneus: Talairach coordinates -2, -80, 46, cluster volume 368 mm^3

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS

Brain volumes in schizophrenia: a meta-analysis in over 18000 subjects

Schizophrenia Bulletin 2012; 39(5): 1129-1138

View review abstract online

Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, mostly inconsistent, direct) suggests decreased parietal grey matter volume in medicated patients.**
Parietal grey matter volume	
Decreased parietal grey matter volume in medicated patients; 9 studies, N = 758, d = -0.31, 95%CI -0.54 to -0.08, p = 7.6 × 10−3, Q = 17.9, p = 0.022, I^2 = 55%	
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct

Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M, Miettunen J

Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis

Human Psychopharmacology 2017; 32: doi: 10.1002/hup.2574

View review abstract online

Comparison	**Association between long-term antipsychotic dose and changes in brain regions over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) found increased antipsychotic dose was associated with decreased parietal lobe volume over time (>2 years).**
Longitudinal changes in parietal grey matter volume	
Small, significant associations between long-term antipsychotic use and; Decreased parietal lobe: 4 studies, N = 370, r = -0.14, 95%CI -0.24 to -0.04, p = 0.007, I^2 = 0% There were no moderating effects of antipsychotic type (first vs. second generation).	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

The “paradoxical” engagement of primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies

Neuropsychologia 2011; 49: 3361-9 View review abstract online	
Comparison	**Functional activation in people with schizophrenia during auditory hallucinations.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activation in the postcentral gyrus and the inferior parietal lobule during auditory hallucinations.**
During hallucinations (endogenously evoked)	
12 studies, N = 103, showed increased activation during hallucinations in; Postcentral gyrus: Talairach coordinates -50, -24, 40, cluster volume 1016mm^3 Inferior parietal lobule: Talairach coordinates 32, -40, 48, cluster volume 960mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kronbichler L, Tschernegg M, Martin AI, Schurz M, Kronbichler M

Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis

Schizophrenia Bulletin 2017; 43: 1240-50 View review abstract online	
Comparison	**Functional activity during theory of mind tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests increased activation in bilateral inferior parietal cortex during theory of mind tasks.**
Functional activity	
21 studies, N = 623	

Increased activation in; Left inferior parietal cortex: 486 voxels, MNI coordinates -42, -48, 38 Right inferior parietal cortex: 405 voxels, MNI coordinates 58, -40, 40	
Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Kühn S, Gallinat J

Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis

Schizophrenia Bulletin 2013; 39(2): 358-365

View review abstract online

Comparison	**Resting-state functional activation in people with schizophrenia vs. controls and in people with major depression vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests decreased activation in the lower precuneus and the precuneus of people with schizophrenia at rest.**
Resting state activity	
11 studies, N = 567 *The following clusters showed decreased activity in people with schizophrenia;* Precuneus (BA7): Talairach coordinates 3, -44, 69, cluster volume 528 Lower precuneus (BA7): Talairach coordinates -6, -70, 35, cluster volume 488mm^3 Lower precuneus (BA23): Talairach coordinates 10, -42, 28, cluster volume 248mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Minzenberg MJ, Laird AR, Thelen S, Carte, CS, Glahn DC

Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia

Archives of General Psychiatry 2009; 66(8): 811-822

View review abstract online

Comparison	**Functional activation during executive functioning tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with schizophrenia show regions of reduced activity in the right inferior parietal region and increased activity in the left inferior parietal region during executive functioning tasks.**
Functional activation	
41 studies, N = 1,217 *Significantly reduced activity in people with schizophrenia in;* Right inferior parietal lobule: Talairach centre of mass 36, -58, 42, cluster volume 792mm^3 *Significantly increased activity in people with schizophrenia in;* Left inferior parietal lobule: Talairach centre of mass -54, -42, 42, cluster volume 1200mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y

Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies

International Journal of Clinical and Experimental Medicine 2017; 10: 1866-78

View review abstract online	
Comparison	**Functional alteration in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, direct, unable to assess consistency or precision) suggests relatives had decreased resting-state brain activity in the left precuneus.**
Functional alterations	
3 studies, N = 214 *Compared to controls, relatives had decreased brain activity in;* Left precuneus: 2,176 voxels, MNI coordinates -4, -54, 42, *p* = 0.00019	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM

Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies

Biological Psychiatry 2011; 70(1): 88-96

View review abstract online

Comparison	**Grey and white matter volume in people with schizophrenia vs. controls**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests no change in parietal grey over time but greater reductions of parietal white matter in people with schizophrenia compared to controls.**
Grey and white matter volume	

Parietal lobe

Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years 31 studies, N = 1,867 *Significantly greater reductions were reported over time in schizophrenia compared to controls in;* Parietal grey matter: N = 364, 7 studies, *d* = -0.161, 95%CI -0.50 to 0.18, *p* = 0.352, I^2 = 52.6% Parietal white matter: N = 227, 4 studies, *d* = -0.533, 95%CI -0.84 to -0.23, *p* = 0.001, I^2 = 4.0%	
Consistency in results	Consistent for white matter, in consistent for grey matter.
Precision in results	Precise
Directness of results	Direct

Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC

Prefrontal activation deficits during episodic memory in schizophrenia

American Journal of Psychiatry 2009; 166(8): 863-874

View review abstract online

Comparison	**Functional activation during episodic memory encoding in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests decreased activity in the right inferior parietal gyrus and increased activity in the left postcentral gyrus during episodic memory encoding.**
Functional activity	
Significantly decreased activity in people with schizophrenia in; Right inferior parietal gyrus: cluster volume 1056mm^3, Talairach centre of mass 50, -48, 36 *Significantly increased activity in people with schizophrenia in;* Left postcentral gyrus: Talairach coordinates -44, -28, 36, cluster volume 344mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ramsay IS, Macdonald AW

Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement

Schizophrenia Bulletin 2015; 41(6): 1276-84

View review abstract online

Comparison	**Functional activation changes in response to cognitive remediation in people with schizophrenia vs. various control conditions. Training duration was an average of 10 weeks comprising 40 sessions.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activity in the right superior parietal lobe and right postcentral gyrus after cognitive remediation.**
Changes in activation	
9 studies, N = 128 *The following clusters showed increases in activation after cognitive remediation;* Right superior parietal lobe: Talairach coordinates 32, -66, 50, cluster volume 448mm^3 Right postcentral gyrus: Talairach coordinates 38, -24, 42, cluster volume 440mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Scognamiglio C, Houenou J

A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia

Australian and New Zealand Journal of Psychiatry 2014; 48(10): 907-16

View review abstract online

Parietal lobe

Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found during cognitive tasks, there was increased activation in relatives in the right parietal precuneus and right inferior parietal lobule. During emotion tasks, there was increased activation in relatives in the left sub-gyral parietal region and the left precuneus, and decreased activation in relatives in the right inferior parietal lobule.**
Cognitive and emotion tasks	
Cognitive tasks 17 studies *The following areas showed increased activation in relatives;* Right precuneus (BA7): Talairach coordinates 14, -66, 52, $p < 0.001$ Right inferior parietal lobule (BA40): Talairach coordinates 54, -32, 34, $p < 0.01$ Emotion tasks: 4 studies *The following areas showed increased activation in relatives;* Left precuneus (BA7): Talairach coordinates -6, -46, 48, $p < 0.01$ Left sub-gyral parietal (BA40): Talairach coordinates -22, -48, 56, $p < 0.01$ *The following areas showed decreased activation in relatives;* Right inferior parietal lobule (BA40): Talairach coordinates 40, -50, 56, $p < 0.01$	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S

Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition

PLoS ONE 2011; 6(10): e25322 View review abstract online	
Comparison	**Functional activation during facial emotion processing in schizophrenia vs. autism spectrum disorders.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) found increased activation in the left inferior parietal region in people with schizophrenia.**
Facial emotion recognition	
17 studies, N = 511 *The following clusters showed increased activation in schizophrenia vs. autism spectrum disorders;* Left inferior parietal: Talairach coordinates -50, -44, -40, cluster volume 360mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Vita A, De Peri L, Sacchetti E

Progressive loss of cortical grey matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies

Translational Psychiatry 2012; 2: e190 View review abstract online	
Comparison	**Volume change over time in longitudinal studies of schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to large samples, mostly precise, inconsistent, direct) suggests medium to large reductions over time in parietal lobe volume of people with first-episode schizophrenia.**
Parietal brain volume	
No differences between groups over time in;	

Parietal GMV: 6 studies, N = 623, *g* = -0.06, 95%CI -0.43 to 0.30, *p* = 0.71, I^2 = 74%, *p* = 0.002 Subgroup analysis of first-episode schizophrenia *Medium to large reductions in volume over time in;* Parietal GMV: 3 studies, N = 490, *g* = -0.30, 95%CI -0.48 to -0.12, *p* = 0.001, I^2 = 0%, *p* > 0.05

Consistency in results	Inconsistent for overall analysis, consistent for first-episode subgroup.
Precision in results	Precise
Directness of results	Direct

Wojtalik JA, Smith MJ, Keshavan MS, Eack SM

A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia

Schizophrenia Bulletin 2017; 43: 1329-47

View review abstract online

Comparison	**Association between functional outcomes and grey matter volume in people with schizophrenia.** **Functional outcomes include global functioning, social functioning, resource needs, quality of life, socioeconomic status, independent living, employment, and role functioning.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found better overall functioning was associated with larger parietal lobe volume.**

Brain volume and functional outcome
37 studies, N = 1,187 *Better functioning was associated with larger volumes in;* Parietal lobe: 5 studies, *r* = 0.29, 95%CI 0.01 to 0.57, *p* = 0.039, Q = 67.29, *p* < 0.001

Consistency in results	Inconsistent, apart from the cerebellum.
Precision in results	Precise
Directness of results	Direct

Parietal lobe

Zhang R, Picchioni M, Allen P, Toulopoulou T

Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies

Schizophrenia Bulletin 2016; 42: 1068-77

View review abstract online

Comparison	**Functional activity during working memory tasks in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) found increased activity in the left inferior parietal lobe of relatives during working memory tasks.**
Functional activity	
15 studies, N = 547 *Increased activity in relatives in;* Left inferior parietal lobe (BA40): Talairach coordinates -40, -60, 44	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, Cheung EFC, Lui SSY, Chan RCK

Neurological soft signs are not “soft” in brain structure and functional networks: evidence from meta-analysis

Schizophrenia Bulletin 2013, doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Brain regions associated with neurological soft signs (NSS) in people with schizophrenia.**

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Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) found reduced grey matter volume in the left postcentral and the inferior parietal lobe were associated with increased severity of NSS. NSS severity correlated with increased activation in the right precuneus.**
NSS	
NSS severity correlated with grey matter volume in: Left postcentral gyrus: Talairach coordinates -48, -26, 52 Left inferior parietal lobe: Talairach coordinates -50, -40, 44 *NSS severity correlated with increased activation in:* Right precuneus: Talairach coordinates 24, -70, 42	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimate, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, DTI = diffusion tensor imaging, FA = fractional anisotropy, fMRI = functional magnetic resonance imaging, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NSS = neurological soft signs, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, Q = Q statistic (chi-square) for the test of heterogeneity, vs. = versus

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Parietal lobe

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[28].

† Different effect measures are reported by different reviews.

ALE analysis (Anatomical Likelihood Estimate) refers to a voxel-based meta-analytic technique for structural imaging in which each point of statistically significant structural difference is spatially smoothed into Gaussian distribution space, and summed to create a statistical map estimating the likelihood of difference in each voxel, as determined by the entire set of included studies. Incorporated with the Genome Scan Meta-analysis (GSMA), the meta-analysis of coordinates from multiple studies can be weighted for sample size to create a random effect analysis. The ALE statistic (if reported) represents the probability of a group difference occurring at each voxel included in the analysis.

Fractional similarity network analysis refers to a network analysis technique in which secondary networks are identified within the larger framework of activity, creating a matrix for regional co-activity.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect [28].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[29]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An *r* of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales. Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[30].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirectcomparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C (2009): Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research* 108: 104-13.
4. Minzenberg MJ, Laird AR, S. T, Carter CS, Glahn DC (2009): Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Archives of General Psychiatry* 66: 811-22.
5. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC (2009): Prefrontal activation deficits during episodic memory in schizophrenia. *American Journal of Psychiatry* 166: 863-74.
6. Chan RCK, Di X, McAlonan GM, Gong Q-y (2009): Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression. *Schizophrenia Bulletin*.
7. Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL*, et al.* (2008): Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry* 64: 774-81.
8. Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM (2011): Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies. *Biological Psychiatry*.
9. Goghari VM (2010): Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimation meta-analysis. *Psychological Medicine* doi: 10.1017/S033291710001972.
10. Alustiza I, Radua J, Pla M, Martin R, Ortuno F (2017): Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit. *Schizophrenia Research* 56: 179-89.
11. Brugger S, Davis JM, Leucht S, Stone JM (2011): Proton magnetic resonance spectroscopy and illness stage in schizophreniaa systematic review and meta-analysis. *Biological Psychiatry* 69: 495-503.
12. Egerton A, Modinos G, Ferrera D, McGuire P (2017): Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis. *Translational Psychiatry* 7: e1147.
13. Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P (2016): Altered Hub Functioning and Compensatory Activations in the Connectome: A Meta-Analysis of Functional Neuroimaging Studies in Schizophrenia. *Schizophrenia Bulletin* 42: 434-42.
14. Gao X, Zhang W, Yao L, Xiao Y, Liu L, Liu J*, et al.* (2018): Association between structural and functional brain alterations in drug-free patients with schizophrenia: A multimodal meta-analysis. *Journal of Psychiatry and Neuroscience* 43: 131-42.
15. Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS (2012): Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophrenia Bulletin* 39: 1129-38.
16. Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J*, et al.* (2017): Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. *Human Psychopharmacology* 32: doi: 10.1002/hup.2574.
17. Vita A, De Peri L, Deste G, Sacchetti E (2012): Progressive loss of cortical gray matter in schizophrenia: A meta-analysis and meta-regression of longitudinal MRI studies. *Translational Psychiatry* 2.

18. Wojtalik JA, Smith MJ, Keshavan MS, Eack SM (2017): A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia. *Schizophrenia Bulletin* 43: 1329-47.
19. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C*, et al.* (2013): Neurological Soft Signs Are Not "Soft" in Brain Structure and Functional Networks: Evidence From ALE Meta-analysis. *Schizophrenia Bulletin*: doi:10.1093/schbul/sbt063.
20. Kompus K, Westerhausen R, Hugdahl K (2011): The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies. *Neuropsychologia* 49: 3361-9.
21. Kronbichler L, Tschernegg M, Martin AI, Schurz M, Kronbichler M (2017): Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis. *Schizophrenia Bulletin* 43: 1240-50.
22. Kuhn S, Gallinat J (2013): Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. *Schizophrenia Bulletin* 39: 358-65.
23. Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y (2017): Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies. *International Journal of Clinical and Experimental Medicine* 10: 1866-78.
24. Ramsay IS, Macdonald AW (2015): Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement. *Schizophrenia Bulletin* 41: 1276-84.
25. Scognamiglio C, Houenou J (2014): A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia. *Australian and New Zealand Journal of Psychiatry* 48: 907-16.
26. Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S (2011): Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS ONE [Electronic Resource]* 6: e25322.
27. Zhang R, Picchioni M, Allen P, Toulopoulou T (2016): Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies. *Schizophrenia Bulletin* 42: 1068-77.
28. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
29. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
30. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*